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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/653,277	Applicant(s) Chiocca et al.
	Examiner Joseph Woitach	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 29, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above, claim(s) *4-12, 34, and 35* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 13, 14, 16-23, 25-31, 33, and 36* is/are rejected.

7) ☒ Claim(s) *15, 24, and 32* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 16
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application filed August 31, 2000, claims benefit to provisional application 60/151,621, filed August 31, 1999.

Applicants' amendment filed January 29, 2003, paper number 16, has been received and entered. Claims 1-36 are pending.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-3, 13-33 and 36, in Paper No. 13 is acknowledged. Claims 4-12 and 34-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. Claims 1-3, 13-33 and 36 are currently under examination.

The requirement is still deemed proper and is therefore made **FINAL.**

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

This application contains claims drawn to an invention nonelected with traverse in Paper No. 13. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

The re-submission of the information disclosure statement filed January 29, 2003, attached to paper number 16, has been received and entered. An initialed and signed copy of the 1449 is provided with this action.

Claim objections

Claims 13 and 30 stand objected to because they contain acronyms for genes/promoters which are not specifically recited in the specification and that they are well recognized in the art.

Applicants point to page 31 of the specification and argue that the acronyms are defined in the specification and well recognized in the art. See Applicants' amendment, bridging pages 3-4. The portions of the specification on page 31 are noted, however these passages do not specifically define the abbreviated terms but rather provide a first presentation of the acronyms. While the claims are read in light of the specification, the metes and bounds of the claims should be defined within the recitation of the claim and be interpreted and stand by themselves. In this case because the specification does not specifically define the abbreviations as encompassing any

specific term, the first presentation of the abbreviated term should be denoted by setting forth the full name indicating the term to be used subsequently.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 24 and 32 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

Applicants note the requirement for deposit of the biological material termed "Myb34.5" and make the declaration under 37 CFR 1.809(b)(1) and (c) that they will make a deposit of the required materia and that deposit complies with 37 CFR 1.801-1.809. Further, it is indicated that after deposit of the vector is made the specification will be amended to reflect the deposit in accordance with 37 CFR 1.809 (d) and (e). See Applicants' amendment, bridging pages 4-5.

Applicants' declaration and statement that a deposit of the Myb34.5 vector will be made is sufficient to overcome the rejection of record. It is noted that upon allowance the deposit will have to properly be made before issuance.

Claims 1-3, 13, 16-23, 25-33 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating tumorigenic disease of the central nervous system and perfuse metastatic liver and colon cancer cells in a mammal comprising administering herpes mutant comprising: (a) an inactivating alteration in the γ34.5 gene and (b) an insertion of a γ34.5 gene under operatively linked to a B-myb promoter, does not reasonably provide enablement for treatment of other types of neoplastic cells or the use of other promoters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants summarize the basis of the rejection and break down their traversal in tow parts: (1) with respect to the products, claims 1-3, 13-16 (pages 5-7); and (2) with respect to the methods claims 17-33, 36 (pages 8-13). With respect to the products Applicants note that claims 14 and 15 recite the "B-myb" and should not be subject to the rejection (page 5). Summarizing the requirements of enablement Applicants point to several decisions and argue that without objective evidence to the contrary the specification should be considered enabled, and that the specification can omit teachings which are well known in the art (pages 6-7). Applicants argue that Myb34.5 represents an exemplary HSV vector and that the specification provides the guidance for the routine experimentation required to make the products as claimed. Further, beyond the use of the vectors *in vivo* applicants argue that the vectors can be used to assay their

own activity in vitro prior to in vivo use (page 7, middle paragraph). With respect to the methods, Applicants argue that requiring a tumor specific promoter enables the use of the vectors for use in the instantly claimed methods (page 8). Further, by providing a cell specific promoter one can selectively target cells known to over express a known cell specific protein (page 9). Applicants argue that the references provided do not demonstrate that HSV vectors have a limited tropism (page 10) and indicate that the inventors have affirmed this position (page 9, final paragraph). Finally, with respect to the broad range of promoters, Applicants argue that it would not constitute undue burden to test the promoters known in the art or specifically recited, and provide a recent publication demonstrating that the direct injection of an HSV vector into a tumor provides a reduction in tumor growth (see Mullen *et al.*) (pages 12-13). See Applicants amendment, pages 5-13. Applicants' arguments have been fully considered but not found persuasive.

With respect to the recitation to "B-myb" Examiner agrees with the limitation encompassed by claim 15 for the specific vector, however claim 14 is broader that the specific B-myb promoter disclosed and encompasses any promoter derived from the gene that encodes B-myb. The specification provides only one specific B-myb promoter which is demonstrated to functional and useful, and is silent with respect to any modified forms of this specific sequence, or to methods of or guidance for modifying this promoter sequence to "derive" a promoter for use in the methods or in the generation of useful products. With respect to any other promoter, there is no guidance for the use of cell-specific promoter with respect to the ability of the HSV

vectors killing a specific tissues. Further, while certain genes are known to be cell specific, their promoters out of context of the gene/genome do not necessarily provide tissue specific expression. However, while Examiner would agree that providing a cell specific promoter could potentially kill a specific tissue, the specification is silent with respect to why a normal tissue would be targeted by the instantly claimed vectors. With respect to cancer related genes and use of their promoters, and in particular the specific promoters recited in the claims (for example claim 13), each of these promoters provides expression in cells other than just tumors. For example PSA is normally expressed by the prostate as well as erb-B2, tyrosinase and MUC1. While CEA and AFP are cancer associated antigens in adults, the promoters when provided in the context of a transgene will be expressed in a wide variety of cells, transformed and non-transformed. The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. See *Ex parte Maizel* 27 USPQ2d 1662 . In the instant case, herpes vectors are known only to infect the cells of central nervous system and metastatic cells of liver and colon origin. Further, the mere recitation of promoters which broadly meet the functional language in light of their endogenous expression does not provide for their use in the artificial context of an HSV vector. The specification is silent with respect to specific guidance for other promoters besides the B-myb promoter to affect expression in neoplastic cells. Further, it is maintained that the specification does not provide the specific guidance on what portions of any other particular promoter one should use and in what types of neoplastic cells one should use said promoters.

With respect to use of the vectors *in vitro*, Applicants arguments for the use *in vitro* to study cytotoxicity *in vitro* before use *in vivo* is a circular argument which affirms the only use of the vectors is for *in vivo* therapy. Examiner would agree that the vectors would be tested *in vitro* before being administered to a subject, however testing for a potential use of a construct is not an enabled use and indicates that the artisan would have to test each of the possible products for their potential usefulness. Further, the specification does not teach that the vectors should be used or would be useful in killing cells *in vitro* for any particular purpose. Killing cells *in vitro* with HSV vectors is not a readily apparent use recognized in the art, and contrary to Applicants' arguments the specification is silent to any apparent use *in vitro* for the instantly claimed products.

With respect to the teachings provided in the Mullen *et al.* reference, Examiner acknowledges that the vectors taught therein are encompassed by the instant claims. However, as noted above the MUC-1 promoter provides expression in a range of cells and provided expression and killed both normal and transformed cells (page 508, middle of second column). Furthermore, a requirement of the vectors encompassed by the claims is the necessity to infect the target cells of interest. In the instant case, the present specification does not provide the necessary teaching to change the tropism of a herpes vector, therefore, the use of such vectors is limited to the delivery and killing of cells of the central nervous system and cells derived from metastatic liver and colon cancer. Additionally, the methods of *in vivo* delivery in Mullen *et al.* are direct injection into the tumor (page 508, second paragraph), wherein the present

specification teaches and Applicants arguments assert that the HSV vectors can be delivered generally, and will be selectively found/expressed by virtue of the tissue/tumor-specific promoter. The methods used by Mullins *et al.* are direct injection into a tumor, and contrary to supporting a general delivery method, the ability of the vector to be expressed in normal and transformed cells teach that tumor promoters require specific delivery methods. Further, as generally argued above, the ability of the HSV vectors to kill both normal and transformed cells *in vitro* indicate that even the specific promoters recited in the claims are not enabled because they would not be selectively expressed. In light of the fact that even the specific species of promoters disclosed and recited in the claims are not enabled for use in the HSV vectors and methods of use indicate that it would constitute an undue burden of testing to make and use the invention as presently claimed because the specific guidance provided is not exemplary of the claimed method. With respect to Myb34.5, Examiner would agree that the specific vector provides a specific combination of promoter/vector sequence which is demonstrated by the working examples to selectively destroy transformed cells. However, in light of the evidence that other promoters, such as MUC1 taught by Mullens *et al.*, are more broadly expressed, it is maintained that it would have required undue experimentation for one skilled in the art to make and use the claimed inventions as broadly claimed.

As noted above, the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. See *Ex parte Maizel* 27 USPQ2d 1662 . The art of record indicates that HSV vectors

are known only to infect the cells of central nervous system and metastatic cells of liver and colon origin, and that the mere recitation of promoters which broadly meet the functional language in light of their endogenous expression does not provide for their use in the artificial context of a vector.

Therefore, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed, and thus the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 13, 14, 16-23, 25-31 and 33 rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza *et al.* (US Patent 5,585,096), Pyles *et al.* (WO 98/42195), Chou *et al.* (Science, 1990), Chambers *et al.* (PNAS, 1995) and Kram *et al.* (Human Gene Therapy, 1997) is withdrawn.

Applicants summarize the basis of the rejection and the basis for making a proper *prima facie* case citing *In re Vaeck* (page 14-15) and argue that there is no teaching or suggestion in the references to delete γ34.5 and then re-insert the γ34.5 under the control of a cell specific or tumor specific promoter. Applicants argue that Maruza and Pyles "teach away" from the claimed invention because γ34.5 is known to affect the neurovirulence and that Examiner has used hindsight reasoning and that Examiner argues that it would have been obvious to try the instantly claimed invention (pages 15-16). Applicants' arguments have been fully considered and are found persuasive in part.

Specifically, it is maintained that the combined teachings of Martuza *et al.*, Pyles *et al.* , Chou *et al.*, Chambers *et al.* and Kram *et al.* provide for the limitations set forth in the claims. Further, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392,

170 USPQ 209 (CCPA 1971). Additionally, because the level of skill in the art is high simply combining and constructing HSV vectors would have been routine, and there would have been an expectation of success (note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988)). However, given that the thrust of the teaching of Martuza *et al.* and Pyles *et al.* is to reduce the virulance of HSV vectors, by deleting γ34.5 and even though *in vivo* γ34.5 provides better killing of cells by increasing the virulence of HSV vectors, Examiner would agree that because of the dangers and problems of the virulence for the *in vivo* use as taught by Martuza *et al.* and Pyles *et al.*, one of ordinary skill in the art would not re-introduce γ34.5 into an HSV vector which was generated to be non-virulent. In particular, many of the specific promoters recited and encompassed by the claims would provide expression in a wide variety of cells, thus the problem of virulence of HSV vectors as discussed by Martuza *et al.* and Pyles *et al.* would again arise. Therefore, even though it was known that γ34.5 provides better cell killing *in vivo* than HSV vectors without γ34.5, the problems of the virulence of these HSV vectors as taught by Martuza *et al.* and Pyles *et al.* would suggest that these vectors are less desirable. Further, because HSV vectors without γ34.5 are capable of killing cells *in vitro*, there is no motivation to re-insert γ34.5 for any use *in vitro* therein avoiding the issue of safety *in vivo* recognized in the art.

Conclusion

No claim is allowed. Claims 15, 24 and 32 are objected to but would be found allowable if rewritten as independent claims incorporating all the limitations of the independent claim and any intervening claim(s). The remaining claims are free of the art of record, however they are subject to other rejections.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Deborah Crouch

Joseph T. Woitach

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630